IgM ELISA value for scrub typhus as a prognostic indicator: our experience in Pediatric and adult cases

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Abstract: Aim of the study: Many studies from various parts of India have reported scrub typhus with diagnosis based on IgM ELISA; however no definite data available for IgM for Scrub Typhus as prognostic indication .Our study gives a correlation of IgM level with the clinical presentations as well as organ involvement and complications thus depicting the prognostication.

Material and methods: - This descriptive observational investigation was carried out over a time of two years. Hospitalized cases with complaints of Indistinct febrile disease with a lymphadenopathy, organomegaly as well as head pain were taken over a period of five days deprived of a recognizable cause. as probable scrub typhus patients and advised for initial Weil- Felix test and scrub IgM level. The spectrum of clinical manifestation and end organ damage were analyzed with scrub typhus serum IgM level.

Results:Among 113 patients diagnosed as scrub typhus basing on IgM value, 48 are children (below 14 yrs) and 65 are adults. Mean age of presentation in children is 3.6 Yrs and adult is 41.5 yrs. Maximum no 43 (26.27%)of patients have IgM value between 2.5 to 3.5 and only five patients have very high value i.e. more than 3.5 . There is significant correlation (P= 0.0027) of presence of clinical and lab finding like rash, eschar, lymphadenopathy, leukocytosis, thrombocytopenia with increasing value of IgM. Among 113 cases, majority had hepatopathy 56(49.5%) followed by nephropathy and sepsis (23.9% each). Only five no of patients have cardiac complications. The percentage of distribution of end organ complications is increasing (P= 0.048) with increasing IgM value except cardiac illness, where the burden is very negligible.

Conclusions: The prognostic indicator of severe disease can be established with increasing trend of serum IgM level with available evidence but a larger study with paired sera will ascertain the correlation..

Keywords: scrub typhus, IgM ELISA, prognostic indicators, Eschar

1. INTRODUCTION:

Scrub typhus seems to be an abrupt febrile onset illness caused through Orientia tsutsugamushi disease defined by lung, back, kidney, CNS including spleen vasculitis. Rickettsial disorders provide physicians with various issues [1]. Usually, because of low apprehension indicator, no particular symptoms and signs, as well as the lack of cheap

diagnostics, those who are extremely hard to diagnose. The degree of clinician skepticism has increased since various recent papers, contributing to more scientific testing, as clinical features for evaluation only become effective within a week and fast medical imaging such as PCR are not easily and inexpensive. In this epidemic, public health priorities are strong [1] where under diagnosis leading to increased fatality rate is up to 30-35% [2],on the other hand irrational use of empirical Doxycycline can increase the adverse effect and chances of resistance . Many studies from various parts of India have reported scrub typhus with diagnosis based on IgM ELISA [3,4],however no definite data is available for IgM being a prognostic indicator for Scrub Typhus. Eschar is pathognomonic for rickettsiosis including scrub typhus, its presence has been reported as an indicator of illness harshness by Vivek et al [5]. Kim et al [6] found absence of eschar to have prognostic significance in their study. Some other study describes low body temperature, rapid pulse rate, presence of crepitation, rLow neutrophil percent, deeased cserum albumin, high aminotransferase aspartate, high creatinine plasma, as well as positive urine albumin mostly as indicator of development gravity [7]. Balasubhramanyam et al found high ESR as marker of bad prognosis[8].Our study gives a correlation of IgM level with the clinical presentation as well as organ involvement and complications thus depicting the prognostication.

2. MATERIAL AND METHODS

This cross sectional observational investigation was passed ready throughout a tertiary attention hospital over a period of two years, July 2016-June 2018. Hospitalized cases admitted in department of pediatrics and medicine with Indistinct febrile disease objections over five days without known cause have been taken, that had yet another or several characteristics such as lymphadenopathy, organomegaly, headache, edema, skin infection, and eschar. as probable scrub typhus patients and advised for initial Weil- Felix test and scrub IgM level. The IgM kit used for testing was obtained from In Bios International Seattle, WA, USA. Cases that were positive (> 0.5 OD serum IgM) for scrub typhus were taken as our cases. Other causes of fever like malaria, dengue, enteric fever, leptospira were excluded from our study by performing confirmatory tests. The clinical presentation, investigation and complications of scrub typhus patients were taken in to account. The spectrum of clinical manifestation and end organ damage were analyzed with scrub typhus serum IgM level.

3. RESULTS

Among 113 patients diagnosed as scrub typhus based on IgM value, 48 are children (below14 yrs) and 65 are adults. Mean age of presentation in children is 3.6 Yrs and adult is 41.5 yrs. Majority belong to 1-5 yrs and 30-45yrs age group(Table 1).The IgM positive values are tabulated with increasing order in Table no-2. Maximum no 43 (26.27%)of patients have IgM value between 2.5 to 3.5 and only five patients have very high value i.e. more than 3.5 OD. Table 3 describes the distribution of clinical picture and few lab parameters with IgM value. 39.8% have lymphadenopathy, 29.2% have eschar and only 18.6% have rash. Leucocytosis is found in 56.6% but thrombocytopenia is not common (18.6%). There is significant (P value 0.045) correlation of clinical and lab finding with increasing value of IgM. Among 113 cases, majority had hepatopathy 56(49.5%) followed by nephropathy and sepsis (23.9% each) . Only five no of patients have cardiac complications. The percentage of distribution of end organ complications is increasing significantly (P value 0.0027) with increasing IgM value except cardiac illness, where the burden is very negligible (Table 4).

Table-1 Distribution of Cases according to age group (n=113)

Age group	Children	Age group	Adult
1 m -1 yr	4	>15-30 yrs	20
>1-5yr	26	>30-45yrs	26
>5-10yr	13	>45-60yrs	15
>10-15yr	5	>60yrs	4
Total	48	Total	65

Table-2 Distribution of Cases according to Scrub typhus IgM value (n=113)

IgM value	Children	Adult	Total
0.5-1.5	12	15	27
>1.5-2.5	23	15	38
>2.5-3.5	11	32	43
>3.5-4.5	2	1	3
>4.5	0	2	2
Total	48	65	113

Table-3 Distribution of presentation according to scrub typhus IgM value (n=113)

IgM value	Total (n)	Rash (n%)	Eschar (n%)	Lymphadenopathy (n%)	Ascites (n%)	Leucocytosis (n%)	Thrombocytopenia (n%)
0.5-1.5	27	6(22.2)	2(7.4)	2(7.4)	0(0)	6(22.2)	2(7.4)
>1.5-2.5	38	6 (15.8)	11(28.9)	13(34.2)	5(13.1)	14(36.8)	5(13.1)
>2.5-3.5	43	8 (18.6)	16(37.2)	25(58.1)	3(7)	39(90.7)	12(27.9)
>3.5-4.5	3	0 (0)	3(100)	3(100)	0(0)	3(100)	2(66.6)
>4.5	2	1(50)	1(50)	2(100)	0(0)	2(100)	0(0)
Total	113	21(18.6)	33(29.2)	45(39.8)	8(7.1)	64(56.6)	21(18.6)

The P-value approach using Annova test: The p-value is p=0.0027

Table-4 Distribution of Complications according to Scrub typhus IgM value

IgM value	Total pts (n)	Nephropathy (n%)	Cardiac (n%)	Hepatopathy (n%)	Encephalopathy(n%)	Pneumonitis/ ARDS (n%)	Sepsis (n%)
0.5-1.5	27	4(14.8)	1(3.7)	15(55.5)	2(7.4)	1(3.7)	1(3.7)
>1.5-2.5	38	7(18.4)	2(5.3)	22 (57.8)	3(7.9)	4(10.5)	7(18.4)
>2.5-3.5	43	12 (27.9)	2(4.6)	28(65.1)	11(25.6)	7(16.3)	14(32.5)
>3.5-4.5	3	2(66.6)	0(0)	3(100)	3(100)	2(66.6)	3(100)
>4.5	2	2(100)	0(0)	2(100)	2(100)	2(100)	2(100)
Total	113	27(23.9)	5(4.4)	60(53.0)	21(18.6)	16(14.2)	27(23.9)

The P-value approach using Annova test: The p-value is p=0.0489

4. DISCUSSION:

Based on the organism and linked pathogen, the prevalence of the symptoms may vary. Several O variations. The severity of tsutsugamushi could vary. The O-induced immune reaction. Tsutsugamushi seems to be attributable to the immunogenicity facilitated both by humor then by cells. The cytokine rise due to the acute infection was well pointed out by Iwasaki et al[9] .The parasite too grew to dodge the protected answer of the host which is leading to high mortality in untreated cases. O tsutsugamushi was found to have Active strategic glycoprotein interpretation 96[10] which can lead the pathogen to neutralize the host response. With this disease, human host with G6pd deficiency had worse prognosis [11,12].

Timely detection of the measures for disease because of the important sequelae unfavorable prognosis is mandatory. Somthayan et al[13] have displayed a strong correlation between higher DNA stack at entry and high death rates, and longer disease duration. The factors associated with mortality have been discussed in Indian context from few tertiary care hospitals. Hypotension requiring vasoactive agents, jaundice, ARDS, need for mechanical ventilation and renal failure with serum creatinine more than 2.5mg/dl were considered as clinical markers of poor prognosis[14] where as hypotension requiring vasoactive agents was considered as independent predictor. Absence of eschar was reported to be a risk factor for high mortality[15] but a recent study described eschar to be associated with poor prognosis in scrub typhus[16]. Among children, G6PD lack, sulphonamide The worse result is correlated with diagnosis, early age, shorter incubation time, lack of rash, diabetes, and late anti-ricketissial medicines institution [17] .

The most appropriate test is PCR or IFA but the PCR based assay will detect the disease till bacteremia persists, before antibody response appears. Because of rural epidemiology, delayed presentation, high cost and non availability of expertise it seems very unlikely that PCR based assay can replace the conventional serology completely. Combined antigen or DNA with antibody response detection may yield a strong diagnostic advantage. ELISA for discovery of IgM antibodies (In Bios global Inc) is now currently available and used in identification of scrub typhus throughout many centers. Tsutsugamushi derived recombinant antigen is used in the test. Infection usually leads to a fast spike of IgM antibodies inside 8 days of the outbreak when a sudden raise of IgG with varying immune system characterizes subsequent or reinfected infection. [18]Irrheumatic factor and untrue bad impacts can give fake good outcomes because of rheumatoid factor may occur in secondary infection where there is sharp rise in IgG level[19].In our study the chances of damage of end organ due to scrub typhus is rising with increasing trend of serum IgM value which can be treated as one of the prognostic indicator. The rise in IgM value correlates significantly (P value 0.0027) with the percentage of patients when clinical factors like rash, eschar, lymphadenopathy, ascites and thrombocytopenia were taken into account. Similarly significant results were also noted (P value 0.048) when organ involvement and complications like nephropathy, cardiac manifestations, hepatopathy, encephalopathy, pneumonitis or ARDS and sepsis were taken into consideration.

There are certain limitations of this study like unable to process paired sample from the same patient at different time to look for the increasing antibody titer and seroconversion. No fixed day of sample collection after symptomatology and using a fixed cutoff value of IgM in different geographical location where the kit has been used as it can vary depending upon the disease prevalence, are also some constraints. The preexisting co-morbid conditions were not recorded properly in adult survey which may increase the chance of end organ damage.

To conclude the harshness of disease rest on on various host besides pathogen linked influences. The clinical pattern, end organ dysfunction and outcome of the disease are dependent on resistant strain, bacterial burden and host immune response in form of IgM antibody production. The prognostic indicator of severe disease can be established with

increasing trend of serum IgM level with available evidence but a larger study with paired sera will ascertain the correlation.

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